REMARKS

Overview

Claims 19, 26, 32, 35, and 39 have been amended. Claims 19-27, 29, 31-33 and 35-39 are now pending in this application. Applicants respectfully request reconsideration of the above-identified application in view of the remarks that follow.

Claim Rejections 35 U.S.C. § 102(b)

Claims 19-27, 29, 31-33 and 35-39 were rejected under 35 U.S.C. § 102(b) as being anticipated by Link et al. (1996) Human Gene Therapy, Vol. 7, 1161-1179. The Examiner further states that "as amended the claims recite methods for treating a tumor and a human subject comprising administering to the subject near the tumor an effective amount of xenogeneic cells having α-(1,3) galactosyl epitopes to activate a hyperacute rejection, thereby treating said tumor." The Examiner states that the claims further "recite wherein the xenogeneic cells are murine vector producing cells, wherein the tumor is an ovarian or peritoneal carcinoma, and wherein the cells are injected into the peritoneal cavity." The Examiner also states that "Link et al teaches the injection of murine HSVtk vector producer cells (VPCs) into the peritoneal cavity to treat ovarian cancer (Link et al., page 1162 in particular)." The Examiner then notes that Link et al states that the introduction of murine HSVtk VPCs "induces a bystander effect and an anti-tumor immune response" (Line et al., page 1162, column 2, paragraph 1). Next the Examiner notes that while Link et al. does not explicitly teach that the murine VPCs have α-(1,3) galactosyl epitopes, it is an inherent and known property of all murine cells derived from wild type mice that they express α-(1,3) galactosyl epitopes. Further, the Examiner states regarding the recitation in the claims that the administration of murine VPCs results in the activation of

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hyperacute rejection and innocent bystander response against the tumor, please note that Link et al. teaches the exact same method steps as recited in the claims. The Examiner then reminds the Applicants that merely discovering and claiming a new benefit to an old process cannot render the process against patentable. *In re Woodruff*, 919 F.2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990); *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). The Examiner also quotes the MPEP stating that "when the claim recites using an old composition or structure and the 'use' is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)" MPEP 2112.02. The Examiner states that Link et at. teaches the same structure recited in the claims, murine VPCs which express α-(1,3) galactosyl epitopes, and further teaches that the exact same method of administering these murine VPCs to treat tumors in humans. Thus, by teaching the same compositions and method steps as the instant claims as written, Link et al. anticipates the instant invention as claimed.

Applicants respectfully submit that the Office Action did not make out a *prima facie* case of anticipation for the following reasons: the reference does not teach each and every claim element nor teach the identical invention in as complete detail as is contained in the claims. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Dillon* 919 F.2d 688, 16 U.S.P.Q.2d 1897, 1908 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991). Applicants respectfully submit that the Link reference does not teach the present invention's claimed bystander effect, anti-tumor immune response, nor the exact same steps to carry out the claimed method without the administration of ganciclovir.

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Applicants respectfully submit that the Office Action did not make out a *prima facie* case of anticipation because the Link reference does not teach each and every claim element. Claim 19 as amended recites "administering to the subject and near the tumor an effective amount of xenogeneic cells having α-(1,3) galactosyl epitopes to activate a hyperacute rejection without administration of ganciclovir, thereby treating said tumor." This limitation is supported by the specification at page 18, lines 15-22, noting the favorable reaction of one patent prior to ganciclovir administration. See also the 37 CFR 1.131 declaration previously submitted with the Amendment After Final Rejection on January 13, 2004. Thus, the Link reference does not teach each element of amended claim 19 because the method described by the Link reference requires gancyclovir and the instant invention does not. Therefore, amended claim 19 is not anticipated by Link. Claims 20-25 depend from claim 19 and are likewise not anticipated by the Link reference since the contain all the limitations of non-anticipated claim 19. Independent claims 26, 32, and 35 as amended now recite similar elements as claim 19 and is patentable over Link et al. for the reasons argued above, plus the elements in the claims.

Examiner states that the Link reference states that the introduction of murine HSVtk VPCs "induces a bystander effect and an anti-tumor immune response" (page 1162, column 2, paragraph 1). Applicants respectfully submit that the Link reference does not teach the element "bystander immune response." Therefore, Applicants respectfully submit that the Office Action did not make out a *prima facie* case of anticipation because the reference does not teach each and every claim element.

Claim 39 as amended recites: "administering xenogeneic cells into the peritoneal cavity of said subject suffering from a metastatic tumor, without subsequent administration of ganciclovir, where said xenogeneic cells activate an immune hyperacute rejection response and a

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bystander immune response against said tumor." Applicants respectfully point out that in the method of the claimed invention, the "bystander" immune response refers to a *secondary immune reaction* against human tumor cells that result as a consequence of a local and very powerful inflammation at the site of injection of xenogeneic cells in the absence of ganciclovir. (emphasis added). Specification, at page 16, lines 13 to 24, which states that the tumor response likely results from the activation of the complement pathway mediated by pre-existing anti-αGal antibodies. Applicants respectfully remind Examiner that Applicants are free to be their own lexicographer and that claims should be interpreted in light of the specification.

In contrast, the Link reference describes the "bystander effect" as referring to the *toxic action* caused by phosphorylated ganciclovir on cells that have not been transduced by retroviral vectors. (emphasis added). Link et al, page 1163, column 1, paragraph 3. In a gene therapy setting involving gene transfer of the HSVtk gene followed by treatment with ganciclovir, some cells are transduced and some cells are not. The cells that are transduced and express HSVtk are capable of phosphorylating ganciclovir which becomes incorporated into DNA, causing interruption of cell division. Phosphorylated ganciclovir is able to diffuse through gap junctions to bystander tumor cells that have not received a copy of the HSVtk gene. The toxicity caused by phosphorylated ganciclovir on these non-transduced tumor cells is known as the "bystander effect." Link et al, at page 1166, column 1, paragraph 1. Thus, the Link reference does not teach each element of amended claim 39 because the bystander effects being described by the Link reference requires gancyclovir and the instant invention does not. Therefore, amended claim 39 is not anticipated by Link. Independent claims 26 and 32 are patentable over Link et al. for the reasons argued above plus the elements in the claims. Claims 27, 29 and 31 dependent on claim 26 are patentable over Link et al. for the reasons argued above plus the elements in the claims.

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Claim 33 dependent on claim 32 is patentable over Link et al. for the reasons argued above plus the elements in the claims. Claim 33 dependent on claim 32 is patentable over Link et al. for the reasons argued above plus the elements in the claims.

Next, Examiner states that the Link reference states that the introduction of murine HSVtk VPCs "induces an anti-tumor immune response." Link et al, at page 1162, column 2, paragraph 1. Applicants respectfully submit that the Link reference does not teach the element "anti-tumor immune response" as disclosed by Applicants and therefore cannot anticipate the claimed invention.

Claim 36 recites: "A method of activating an immune response against a tumor in a human subject, the method comprising: administering into the peritoneal cavity of said subject an effective amount of xenogeneic cells of murine origin, thereby activating a hyperacute rejection response capable of attacking said tumor, wherein said tumor exhibits disseminated metastases."

Applicants respectfully point out that in the method of the claimed invention, the "anti-tumor immune response" does not require gancyclovir. Rather, the claimed invention requires the use of $\alpha(1,3)$ galactosyl positive xenogeneic cells as the immunogen, in humans recipients that have pre-existing anti-αGal antibodies. Specification, at page 16 which states that the tumor response largely results from anti-αGal antibodies activating the complement pathway. The method of the claimed invention can make use of any xenogeneic cell (normal or tumor) of any animal origin (murine, porcine, bovine, etc). Specification, at pages 13 and 18. The method of the claimed invention does not involve the use of vector producer cells or gene transfer or treatment with ganciclovir.

In contrast, the Link reference describes the "anti-tumor immune responses" as being triggered by cell debris resulting from dying tumor cells as a consequence of HSVtk-ganciclovir

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treatment. Furthermore, contrary to the method of the present invention, the anti-tumor immune response observed by Link et al after HSVtk-gancyclovir treatment is not mediated by pre-existing antibodies anti-αGal, does not result in activation of the complement pathway and does not trigger Fc-receptor mediated uptake of antibody-antigen complexes by antigen presenting cells, thereby resulting in a mild response mediated only by the presence of subtle allogeneic differences between the recipient animals and the tumor cell lines used in the study. The evidence for an anti-tumor immune response arising from tumors treated with HSVtk-ganciclovir was obtained in mice and rats, which are both α (1,3) galactosyl positive animals that do not develop an hyperacute response against cells expressing α (1,3) galactosyl epitopes. Link et al, at page 1165, column 2, first full paragraph. Moreover, the immune response to which the Link reference refers to requires previous gene transfer and expression of HSVtk, which is not the case in the method of the claimed invention. Thus, the Link reference does not teach each element of amended claim 36 because the immune response described in Link et al requires the presence of ganciclovir. Therefore amended claim 36 is not anticipated by Link. Claims 37-38 dependent on claim 36 is patentable over Link et al. for the reasons argued above plus the elements in the claims.

The Examiner states that the paper by Link et al "teaches the exact same method steps as recited in the claims." Applicants respectfully disagree and points out that the method steps are different. Therefore, Applicants respectfully submit that the Office Action did not make out a *prima facie* case of anticipation because the reference does not teach each and every claim element.

The method of the claimed invention can make use of any xenogeneic cell (normal or tumor) of any animal origin (murine, porcine, bovine, etc). Specification, at pages 13 and 18.

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The method of the claimed invention does not involve the use of vector producer cells or gene transfer or treatment with ganciclovir.

In contrast, the Link reference describes the injection of vector producer cells LTKOSN.2 that direct the production of retrovirus encoding HSVtk, followed by the administration of ganciclovir. Moreover, the Link reference describes the use of a murine cell line, only if this cell line is capable of producing the retrovirus encoding the HSVtk gene. The implementation of this method requires effective *in vivo* gene transfer followed by ganciclovir administration. Thus, the Link reference does not teach each element of amended claims 19, 26, 32, and 39, which recite similar elements with respect to the limitation of treatment without ganciclovir, or teach each element of claim 36, which contains no negative limitation with respect to ganciclovir, because the method of the claimed invention is a purely immunologic approach for the treatment of tumors. In contrast, the method described in the Link reference is a chemotherapeutic approach that requires prior gene transfer and ganciclovir. For these reasons, Applicants believe that amended claims 19, 26, 32, 35, and 39 and claim 36 are not anticipated by Link. Claim 20-25 dependent on claim 19 are patentable over Link et al. for the reasons argued above plus the elements in the claim. Claims 27, 29 and 31 dependent on claim 26 are patentable over Link et al. for the reasons argued above plus the elements in the claims. Claims 37 and 38 depend from claim 36 and are patentable over Link et al. for the reasons argued above plus the elements in the claims. Applicants respectfully request that the rejection of the claims 19-27, 29, 31-33 and 35-39 under 35 U.S.C. § 102(b) be withdrawn and reconsidered.

Conclusion

In light of the above amendment and remarks, Applicants assert that the claims as amended are in a condition for allowance. Applicants respectfully request reconsideration and

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withdrawal of the above rejections to claims 19-27, 29, 31-33 and 35-39.

No fees are believed to be due in connection with this amendment; however, consider this a request for any inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

HEIDI S. NEBEL, Reg. No. 37,719
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No: (515) 288-3667
Fax No: (515) 288-1338
CUSTOMER NO: 22885

Attorneys of Record

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